REMARKS

Claim 58 was rejected under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. In order to expedite prosecution of the present application, Applicant has canceled claim 58 making this rejection moot.

Claims 27-31, 33-42 and 48-57 are rejected under 35 U.S.C. § 103 as being unpatentable over Nahoum in view of El-Rashidy, Lowrey and Reilly.

Prima Facie Case of Obviousness Is Not Met

The Manual of Patent Examining Procedure (MPEP) sets forth the 3 basic criteria that must be met to establish a prima facie case of obviousness. As set forth in the MPEP §2143, these requirements are:

1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or to combine reference teachings;

2) There must be a reasonable expectation of success; and

3) The prior art reference or references when combined must teach or suggest all of the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in Applicants' disclosure. MPEP §2143 citing *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). Indeed, the Examiner must cast the mind back to the time of the invention "to consider the thinking of one of ordinary skill in the art, guided only by prior art references and the then accepted wisdom in the field." *In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313 (Fed. Cir. 2000). Proper application of the basic criteria illustrates that the current rejection fails to meet all three of these criteria, any one of which justifies rescission of the pending rejection.

No suggestion or motivation to modify the reference teachings

Nahoum teaches "The present invention provides for the use of a histamine H_2 receptor agonist and/or a histamine H_3 receptor agonist, or pharmaceutically acceptable salts thereof, alone or in combination with other agents, for the treatment of erectile dysfunction's in animals, and human beings."(col.2, lines 36-41) The invention claimed by Nahoum is clearly set forth in claim 1, "A method of treating sexual dysfunction in a mammal in need thereof which comprises administering to said mammal an effective amount of H_3 agonist." In order to establish prima facie obviousness of Applicants' invention the Examiner must identify in the prior art a suggestion or motivation to modify the teachings of Nahoum so as to replace the primary active agent of a H_3 agonist with a different primary agent, in particular, misoprostol or misoprostol and alprostadil in combination. The Examiner points to absolutely no motivation or suggestion in the cited references to make this modification to Nahoum.

The three other cited references El-Rashidy, Lowrey and Reilly do not even mention misoprostol. Thus, it is not seen how any of the three references could teach one of ordinary skill in the art to substitute misoprostol for H_3 agonist as the primary active agent. None of the cited references make mention that misoprostol has an ability to penetrate skin that makes it uniquely suitable for use in a topical composition for the treatment of female sexual dysfunction. Thus, again the prior art lacks the suggestion or motivation for using misoprostol rather than H_3 agonist as a primary active agent in a topical composition. These contributions of the inventors, not found or suggested by the prior art need to be rewarded with an allowance.

The Examiner concedes that "Nahoum does not expressly teach the application of the topical prostaglandin composition in a method of treating female sexual dysfunction to the vagina or clitoris." The Examiner argues that topical treatment of female sexual dysfunction is shown in Nahoum at column 10, lines 48-49, but when one refers to this section of the patent there is no mention of female treatment at all. Rather the sentence refers to erectogenic agents and suggests intraurethral administration as one of the alternatives. Female treatment is not addressed. Thus, in order to reject the claims, motivation or suggestion must be found in the cited references for use of misoprostol in a topical

composition for the treatment of female sexual dysfunction. El-Rashidy lacks any discussion of the treatment of females or female sexual dysfunction treatment. Reilly also does not discuss female sexual dysfunction. Lowrey is directed to oral administration of therapeutic agents.

These references lack the necessary suggestion or modification of Nahoum to use misoprostol in a topical composition to treat female sexual dysfunction. Not only do the cited references fail to provide the necessary suggestion or motivation to modify Nahoum as the Examiner has done, but the wisdom at the time of Applicants' invention actually taught away from using misoprostol in a topical administration for females. As set forth in the patent application at page 7, lines 13-15, the Physician's Desk Reference recognized that misoprostol causes irritation of smooth urethral fibers. This raises concerns for using misoprostol in touch with the genital system of pregnant women. At certain dosage levels, it could cause miscarriage. The examiner has not overcome the common wisdom teaching away from Applicants' invention. There is no suggestion to replace the primary agent in Nahoum, nor is there any suggestion to use misoprostol in a topical composition and more particularly, no suggestion to use a misoprostol topical composition to treat female sexual dysfunction. For any of these reasons, the claims should be allowed.

No Reasonable Expectation of Success

Applicants also assert that there was no reason in the cited art to expect that misoprostol would make an effective topical treatment for female sexual dysfunction. Nahoum provided no test results (let alone successful test results) on female subjects. Nahoum had no discussion of topical administration to the clitoris or vagina. Thus, Nahoum which teaches the use of H_3 agonist provided no reasonable expectation of success with Applicants' invention. El-Rashidy lacks any discussion of the treatment of female sexual dysfunction. Reilly also does not discuss female sexual dysfunction treatment. Lowrey does not discuss the use of misoprostol nor topical administration of therapeutic agent to treat female sexual dysfunction. Lowrey provides no test results with women from which to establish an expectation of success. At best, Lowrey, in example 5, gives a mere prophetic example suggesting that one might try using an oral formulation with female subjects. Thus, there is an absolute dearth of support for the required finding of a reasonable expectation of

success for topical treatment of female sexual dysfunction with misoprostol. Prima facie obviousness therefore has not been established.

Moreover, at the time of Applicants' invention rather than a reasonable expectation, the state of the art in general involved a great deal of unpredictability. None of the cited references single out misoprostol as an effective topical treatment for female sexual dysfunction. The Examiner relies on a list of "therapeutically active compounds" in column 10, which includes PGE-1 and yohimbine. The Declaration in Support of Applicants' Response dated October 11, 2002 was previously submitted and showed data from female sexual dysfunction studies in which topically applied misoprostol was substantially superior to PGE-1. Also, an article previously submitted entitled "Plasma MHPG: Response to Yohimbine Treatment in Women with Hypoactive Sexual Desire" published in a January-March 1998 Journal of Sex and Marital Therapy concluded that women demonstrated no therapeutic response to yohimbine. Just because a substance appears on the list in column 10 of Nahoum does not mean that there was any reasonable expectation of successfully treating female sexual dysfunction, either topically or otherwise.

Nahoum merely provides a list of compounds without indicating which if any would form an effective topical treatment for female sexual dysfunction. "If it is necessary to go through the long list of compounds... to determine whether they are suitable,.... the patent has no anticipative value. In some cases, even though the prior art does teach that the members of a class are generally equivalent to a member or members disclosed, if it develops through a subsequent research that some one member or members of the class are highly superior to others and therefore not mere equivalents, a second patent may properly be granted." *Ex parte Bauer*, 23 U.S.P.Q. 322 (1934 Pat. Off. Bd. App.) Thus, in view of the Declaration in Support of Applicants' Response dated October 11, 2002, the superiority of misoprostol over other list member PGE_1, calls for allowance of the claims. Also, the lack of therapeutic response from other list member yohimbine, further argues for allowance of claims directed to use of misoprostol.

Furthermore, the cited references have not demonstrated during the relative time period, a reasonable expectation of success with a topical composition. In November 1997 Buyuktimken et al. described the state of the art as lacking an effective topical composition containing prostaglandin E_1:

> While the potential benefits for transdermal delivery of prostaglandin E_1 have longed been recognized, prior efforts at developing a topical composition for prostaglandin delivery have not been fully successful. (Col. 1, lines 29-33)

Thus, at the time of Applicants' invention the Examiner has not shown reason to expect success with a topical composition. More particularly, there has been shown no reason to expect success in the treatment of female sexual dysfunction. Further results would have been quite unpredictable when selecting any of the compounds identified in the list provided by Nahoum. A finding of obviousness requires that the prior art show a reasonable expectation of success. *Amgen, Inc. v. Chugai Pharmaceuticals, Co., Ltd.,* 18 U.S.P.Q. 2d 1016, 1022 (Fed. Cir. 1991). The absence of a reasonable expectation of success precludes a finding of prima facie obviousness. Therefore, the claims should be allowed.

Missing Claim Limitations

Referring now more specifically to the claims, all of the claims should be allowed for the reasons cited above with regard to the failure of the prior art to provide a suggestion or a motivation to modify Nahoum and the lack of a reasonable expectation of success for any such modification. In addition, a prima facie case requires that the references teach or suggest every one of the claim limitations. This has not been shown.

Claim 27 is directed to a vasoactive formulation in which the primary vasoactive agent is misoprostol or misoprostol acid. None of the references show this limitation. While Nahoum describes a pharmaceutical composition, it merely includes misoprostol in a list of possible therapeutically active compounds to use along with the essential ingredients of the composition. Nahoum provides no indication, suggestion or motivation for making misoprostol the primary vasoactive agent. The other references, El-Rashidy, Lowrey and Reilly do not even mention misoprostol and therefore fail to satisfy this deficiency in Nahoum. For this additional reason, claim 27 must be allowed.

Claim 27 further recites topical administration to the clitoris and vagina. The cited references do not provide an enabling disclosure of a treatment for female sexual dysfunction involving a topical application of vasoactive agent onto the vagina or clitoris. To the extent that the Examiner makes statements relying on those of ordinary skill in the art having some familiarity with this treatment, there is no support for that on the record. The Examiner says

"It would have been obvious for one of ordinary skill in the art at the time of the invention was made to apply a topical female dysfunction treating composition of misoprostol ...onto the vagina or clitoris." Such statement may not legitimately support a rejection of the claims unless the Examiner is able to present an Affidavit fully complying with the requirements of 37 C.F.R 1.104 (d)(2). This rule reads as follows:

> When a rejection in an application is based on facts within the personal knowledge of an employee of the office, the data will be as specific as possible, and the reference must be supported, when called for by the Applicant, by the affidavit of such employee, and such affidavit will be subject to contradiction or explanation by the affidavits of the Applicant and other persons.

Lacking such an Affidavit, the cited art fails to make an enabling disclosure of a topical administration to the clitoris or vagina. For this further reason, claim 27 should be allowed.

Claim 41 requires topical administration of a mixture including misoprostol or misoprostol acid to a female subject for the treatment of sexual dysfunction. None of the references disclose this limitation. Although Nahoum makes mention of a possible topical composition and in other areas of the patent suggests that H_3 agonist can also be used to treat women, Nahoum fails to provide an enabling disclosure as to what treatment might work for female sexual dysfunction. The in vivo experiments described relate solely to erectile dysfunction in males. The generic description of topical formulations in column 10, line 65; col. 11, line 7 and enhancers (col. 14, line 9; col. 15, line 58) does not provide specific guidance to one of ordinary skill in the art as to how these reagents should be used and to what effect. For example, the use of ethanol as a solution or additive is described in column 12, line 38 and 51, and yet ethanol in inappropriate amounts could be extremely painful when applied to the clitoris or vagina. Dimethyl sulfoxide (DMSO) is recommended as a solvent or an enhancer (col. 12, l. 41; col. 14, line 17). Yet DMSO is also problematic "...this carrier [DMSO] has not been approved for use by the U.S. Food and Drug Administration. Moreover, DMSO also has the undesirable effect of enhancing the systemic absorption of the vasodilator." (El-Rashidy, col. 2, line 51-58). Nahoum gives no examples or guidance as to what sort of formulation can be used for females, what treatment can be used or what components should go into a formulation for treating females. To the extent that topical formulations are described by Nahoum, they are described for use in treating erectile dysfunction. While Nahoum makes random mention of using its invention for women,

Nahoum does not enable one of ordinary skill in the art by providing a suitable composition and identifying an administration procedure with a reasonable expectation of success in women. The other references fail to satisfy these deficiencies. Because of these missing limitations and the lack of a prima facie case of obviousness, claim 41 should be allowed.

The Examiner asserts that "Applying a composition containing known vasodilating agents, including the instant compounds directly onto any area of the genital would have been reasonably expected to be effective in causing vasodilatation and engorgement of the genitalia: and thereby treating female sexual dysfunction." There is no support for this statement in these cited references. The references give no successful results with female sexual dysfunction. The references do not explain how to prepare a topical composition so that it is not irritating to the clitoris or vagina. In particular, the references do not explain how to use misoprostol, known to be irritating to smooth urethral fiber, in a topical composition for treatment of female sexual dysfunction. The references do not identify how to apply that which was learned from injection treatments into a male urethra and other intraurethral treatments and transferring knowledge from those treatments to use with women. The conclusions set forth by the Examiner are unsupported by references. To the extent that the Examiner is relying upon personal knowledge, an Affidavit pursuant to 37 C.F.R 1.104 (d)(2) is required. To the extent the rejection of claim 41 or any of the other claims is supported in whole or in part by the Examiner's assertion, these claims must be allowed in the absence of such an affidavit.

Claim 42 recites a dosage of misoprostol or misoprostol acid in the range of 0.3-0.9%w/v. The cited references provide no teaching of this amount of misoprostol in a mixture for topical administration. Rather than cite to prior art, the Examiner merely states that "one of ordinary skill in the art would have been motivated to apply the sexual dysfunction treating composition, employing misoprostol in the amount of 0.3-0.9%..." There is no support in the cited prior art for this statement. As for misoprostol, the Examiner further states that "these agents are known to be useful in the treatment of sexual dysfunctions, including in females." None of the cited references give examples of successful treatment of female sexual dysfunction. None of the cited references provide an enabling disclosure of a topical treatment for female sexual dysfunction. The Examiner's statements with respect to use of misoprostol in the amount of 0.3-0.9% and the purported

known usefulness in the treatment of female sexual dysfunction are made solely on the Examiner's supposition or knowledge. Applicants must insist that the Examiner support these rejections with a suitable Affidavit pursuant to 37 C.F.R 1.104 (d)(2). In the absence of prior art to support the rejection, claim 42 should be allowed as well.

Claim 48 is directed to a topical formulation including an effective dose of misoprotol compound and alprostadil. Penetration of the alprostadil to underlying tissue is facilitated by the misoprostol compound. None of the references cited by the Examiner suggest taking advantage of the penetration enhancing properties of misoprostol. To the extent that Nahoum suggests a combination of drugs, there is no suggestion nor motivation to combine misoprostol and alprostadil. As to combinations, Nahoum states "in combinations of two or more drugs, such a PGE_1 and the α–blockers tend to potentiate the erectile effect, thereby permitting efficacy to be obtained at a lower dose of both drugs." (col. 19, lines 19-22). The suggestion to use a combination is with respect the α–blockers and not a combination of misoprostol and alprostadil. Moreover, a combination is suggested for use with erectile dysfunction, rather than for use on female sexual dysfunction. There is no suggestion, disclosure or motivation to use misoprostol for its penetration enhancing properties. Thus, there is no suggestion, disclosure or motivation in the cited references to use the claimed combination of drugs in a formulation and indeed no suggestion to use the combination in a topical formulation. For these additional reasons, claim 48 should be allowed.

Claim 50 is further directed to the use of misoprostol or misoprostol acid in a vasoactive formulation without a non-misoprostol penetration enhancer. None of the references cited by the Examiner provide any suggestion that misoprostol or misoprostol acid have penetration enhancing properties that make them particularly suitable for topical administration to treat female sexual dysfunction. Whereas the claimed invention lacks a non-misoprostol penetration enhancer, Nahoum teaches away from this invention by recommending such a penetration enhancer. Nahoum states, "It may be necessary to use an absorption or penetration enhancers in the various compositions used herein." (col. 14, lines 8-9) Thus, Nahoum teaches away from the penetration enhancing properties of misoprostol as claimed in claim 50 and claim 48 discussed above. Because of these missing limitations

and those recited for claim 41 and for the lack of a prima facie case of obviousness, claim 50 should be allowed.

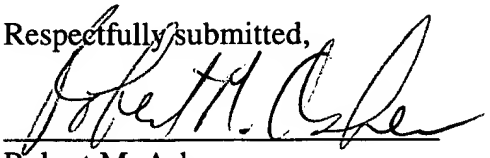
Claims 55 and 56 were newly added to the application with the filing of the RCE. In claim 55, the vasoactive formulation is more particularly recited as "consisting essentially of misoprostol and/or misoprostol acid." Claim 56 recites "the active agent consisting of misoprostol and/or misoprostol acid." Nahoum teaches a formulation in which the active agent is primarily an H_3 agonist. The Examiner points to no art to suggest modifying Nahoum by removing the active agent that Nahoum claims as its invention. The Examiner apparently overlooks that claims 55 and 56 are new claims in which the active agent is strictly defined. This fully distinguishes Nahoum in which the H_3 agonist predominates as the erectogenic agent. The Examiner's statement that "one of ordinary skill in the art would have been motivated to apply the sexual dysfunction treating composition, employing misoprostol... without another vasodilator" is entirely at odds with the disclosure of Nahoum. To the extent that this suggestion comes from the Examiner's own personal knowledge. A suitable Affidavit pursuant to the 37 C.F.R 1.104 (d)(2) is required. Nahoum is the only one of the four references that even mentions misoprostol, but Nahoum clearly teaches against using misoprostol as the active agent in place of a H_3 agonist. For these additional reasons, claims 55 and 56 should be allowed.

Claim 57 recites a topical formulation in which the active agent consists essentially of a mixture of a misoprostol compound.and alprostadil. As with claims 55 and 56 discussed above, Nahoum is directed to formulations in which the active agent consists primarily of H_3 agonist. Nahoum does not disclose a mixture of misoprostol compound and alprostadil. Nahoum does not disclose, suggest or teach substituting misoprostol compound and alprostadil for H_3 agonist as the primary active agent. As discussed with respect to claims 55 and 56, claim 57 should be allowed.

The Examiner responded to the Declaration of inventor Karouzakis as if it were filed under Rule 132 to distinguish the effectiveness of misoprostol against the closest prior art. To the contrary, Dr. Karouzakis' declaration was submitted under Rule 131 in order to swear behind Place et al. and Buyuktimken et al.

For all of the foregoing reasons, Applicants submit that all pending claims in the present application are overwhelmingly allowable over the art of record and early notice to that effect is respectfully solicited.

Respectfully submitted,



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